REMARKS

This paper is a Response to the Office Action mailed April 1, 2011. Claims 28 to 45 are pending and under consideration. Claim 33 has been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. New claims 48 to 50 have been added. Accordingly, upon entry of this Response, claims 28 to 32, 34 to 45, and 48 to 50 are under consideration.

Regarding the Oath/Declaration

Applicants submit the original oath executed by the Applicants which identifies the citizenship of each inventor. The previously submitted oath was submitted without the second page of the document, and the submission also inadvertently included the second page of the assignment document. Applicants believe that the original oath is in compliance with 37 C.F.R. § 1.67(a).

Regarding the Objection to the Specification and Drawings

The specification has been amended to address formalities, namely to add sequence identifiers (SEQ. ID NOs.), to renumber drawing figures 19 to 26, to insert section headings, and to direct the sequence listing's entry into the application to comply with rules for sequences submitted electronically and in order to comply with sequence requirements. Submitted herewith is a computer readable copy of the Sequence Listing. An executed statement under 37 C.F.R §1.821(f) and (g) that the paper and computer readable copies of the Sequence Listing are identical, and that the Sequence Listing does not add new matter, is also submitted herewith. Also, submitted herewith are corrected Drawing sheets. Accordingly, as the amendments were made to address formalities, no new matter has been added and entry of the Sequence Listing, amendments and corrected drawings is respectfully requested.

Regarding the Claim Amendments

The claim amendments are supported throughout the specification or were made to address informalities. In particular, the amendment to claim 28 to recite "depletion or removal" of "tumor necrosis factor receptor (TNFR) from blood or blood fractions" is

supported, for example in Example 3 at page 64, line 13, to page 65, line 7. The amendment to claim 28 to recite "tumor necrosis factor (TNF) monomer" is supported, for example at page 5 lines 21 to 24. The amendment to claim 28 to recite "under conditions allowing binding of TNFR in the blood or the blood fraction to the surface or particle" is supported, for example at page 29, lines 5 to 13. The amendment to claim 30 to recite "injected or" is supported, for example at page 29, lines 15 to 22. The amendment to claim 32 to recite "the blood or the blood fraction" was made in view of the amendment to claim 28. The remaining amendments were made to conform the claims to the amended language of claim 28 and to correct antecedent basis thereby addressing informalities. Thus, as the claim amendments are supported throughout the specification or were made to address informalities, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 48 to 50 are supported throughout the specification. In particular, claims 48 to 50 are supported, for example, by originally filed claims 41, 44 and 45. Thus, as claims 48 to 50 are supported throughout the specification, no new matter has been added and entry thereof is respectfully requested.

Rejection under 35 U.S.C. 112, second paragraph

The rejection of claims 28 to 45 under 35 U.S.C. §112, second paragraph, as allegedly indefinite, is respectfully traversed. The grounds for rejection are set forth in the Office Action at pages 6 to 9.

Claim 28 has been amended to delete the alternative use of "and/or," to provide sufficient antecedent basis for "the blood," to more clearly define what is being depleted or removed from blood or blood fractions, and to more clearly define the step that relates back to the preamble. Claim 30 has been amended to provide sufficient antecedent basis for "the thus treated blood or blood fraction" and to more clearly define the "blood or blood fraction reinjected into a patient." Claim 33 has been cancelled and therefore the rejection to this claim is moot. Claim 43 has been amended to provide sufficient antecedent basis for "the cell surface." Claims 41, 44, and 45 have been amended to eliminate the broad range or limitation together with a narrow range or limitation that falls within broad range or limitation.

In view of the foregoing amendments to address informalities, and not for reasons related to patentability, claims 28 to 32, and 34 to 45 are clear and definite under 35 U.S.C. §112, second paragraph. Consequently, Applicants respectfully request that the rejection under 35 U.S. C. §112, second paragraph, be withdrawn.

Rejections under 35 U.S.C. 112, first paragraph, enablement

The rejection of claims 28 to 45 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The grounds for rejection are set forth in the Office Action at pages 9 to 15.

The claims are adequately enabled prior to entry of the Response. Nevertheless, without acquiescing to the propriety of the rejection and solely in order to further prosecution of the application, claim 33 has been cancelled herein without prejudice rendering the rejection moot, and claims 28 to 32, and 34 to 45 have been amended. The rejection will therefore be addressed insofar as it may pertain to claims 28 to 32, and 34 to 50 upon entry of the Response.

(i) Binding of blood or blood fractions expressing TNFR to a surface/particle coupled to a polypeptide, Separating depleted/removed TNFR in the blood or blood fractions; and Usefulness of Injecting or reinjecting the separated blood or blood fraction

First, regarding the rejection at page 10 due to the specification not providing methods or working examples that indicate the binding function of the polypeptide, amended and new claims 28 to 32, and 34 to 50 recite binding of the blood or blood fractions expressing TNFR to a surface or particle coupled to a polypeptide wherein the polypeptide comprises at least three TNF monomer components and at least two peptide linker components. Applicants respectfully direct the Examiner's attention to the accompanying Declaration under 37 C.F.R. §1.132, executed by Dr. Larry Wiese, and Exhibit A, submitted herewith. In the Declaration, Dr. Wiese describes studies of TNFR depletion and removal from blood and the data is summarized in Exhibit A. In particular, the data in Exhibit A shows that a single chain tumor necrosis factor (scTNF) comprising three tumor necrosis factor (TNF) monomers linked together by two peptide linkers and immobilized to the surface of microporous beads performs as claimed (Declaration, paragraph 6). A filter device with microporous beads with

immobilized scTNF was analyzed for the removal/depletion of tumor necrosis factor receptor (TNFR) (Declaration, paragraph 8). First, serum or PBS spiked with TNFR was passed through the filter device (Declaration, paragraph 9). The TNFR in the serum or PBS binds to the coupled scTNF immobilized on the surface of the microporous beads in the filter device (Declaration, paragraph 9). This, in turn, leads to removal/depletion of TNFR from serum and from PBS (Declaration, paragraph 9) as the fluid passes through the filter device, as shown in Exhibit A, a bar graph showing reduced amounts of TNFR. Accordingly, the Declaration and accompanying data in Exhibit A show that TNFR in blood or in blood fractions is removed or depleted by the scTNF coupled to the surface or particle.

Second, regarding the rejection at page 11 due to the specification not providing methods or working examples that indicate the separation of the bound, suspended, or cellular blood components, Applicants again direct the Examiner's attention to the Declaration under 37 C.F.R. §1.132 and accompanying Exhibit A. Exhibit A shows the removal/depletion of TNFR from the serum and PBS by the filter device (Declaration, paragraph 10). As illustrated in Exhibit A, the two filter devices significantly removed/depleted TNFR from the serum and PBS, by about 90% (Declaration, paragraph 10). Thus, the data corroborates that TNFR in blood or blood fractions is depleted/removed as claimed.

Further, in terms of separating depleted/removed TNFR in the blood or blood fractions, the specification discloses, and the Examiner acknowledges, that "extracorporeal (*ex vivo*) manipulation, depletion, and/or removal of components in body fluids, such as, e.g., binding partners of a component A, as defined above, or cells binding thereto or associated therewith. Such extracorporeal methods comprise preferable methods such as, e.g., apheresis, particularly the basic forms of apheresis, plasmapheresis and cytapheresis" (page 27, lines 9 to 13). Further, "Plasmapheresis according to the invention includes extracorporeal manipulation, depletion, and/or removal of certain soluble or suspended components in the plasma fraction of blood, and the return of the thus treated blood to the patient. To do this, peripheral blood is removed from a patient preferably by means of a pheresis machine; anticoagulant agents are optionally added to the blood, and the blood is separated into its major components—solid (red blood cells, white blood cells, and platelets) and liquid fractions (plasma). After separation into these main components, the soluble or suspended blood components, present in the thus obtained plasma fraction, can be

manipulated, depleted, and/or removed in another process step, for example, with use of the polypeptides of the invention. Next, the thus treated blood plasma together with the previously separated solid blood components can be combined and reinjected into the patient. The volume loss due to the plasmapheresis can be later replaced by isotonic saline solution in the method of the invention. Plasmapheresis as taught by the invention is preferably carried out with the use of methods such as therapeutic plasma exchange (TPE), immunabsorption (IA), precipitation (HELP), differential membrane filtration, and other means." (page 27, lines 15 to 30). Thus, the specification discloses methods of apheresis, plasmapheresis and cytapheresis that can be used by one skilled in the art to deplete/remove TNFR in blood or blood fractions without undue experimentation.

Third, in terms of the Examiner's concern on page 11 that the specification does not disclose that treated blood or blood fraction is injected or reinjected or why the treated blood or blood fraction would be injected or reinjected, Applicants believe that such an argument is not a basis for an enablement rejection, but perhaps instead a 35 U.S.C. §112, second paragraph rejection. Nevertheless, Applicants point out that the specification discloses, for example, that "the members of the TNF ligand family or their membrane receptors can be used variously for the treatment of numerous diseases, such as infectious and inflammatory diseases, metabolic diseases, diseases based on defective regulation of apoptosis, neurodegenerative diseases, and many other diseases. Their use in the treatment of cancer diseases plays an especially important role, because members of the TNF ligand family are usually substances exhibiting antitumor activity. To be noted in particular in this regard are TNF itself (Eggermont, A.M. and ten Hagen, T.L. (2003), Curr. Oncol. Rep. 5, 79-80)..." (page 3, lines 4 to 11). Thus, one of skill in the art, in view of the guidance in the specification, would know how to inject or reinject treated blood or a blood fraction into a patient without undue experimentation.

In sum, in view of the accompanying Declaration, data and guidance in the specification showing that blood or blood fractions expressing TNFR can have TNFR depleted/removed by a surface or particle coupled to scTNF as claimed, the claims are adequately enabled.

(ii) Functional/Biological activity of the polypeptide and use thereof

Regarding the ground for rejection at page 12, namely, that the specification does not teach any methods or working examples that indicate different TNF ligand family monomers (and even different species of TNF ligand family monomers) together generate a functional single chain monomer protein, and thus, one of skill in the art would not be able to predict that all possible permutations of the polypeptide encompassed by the instant claims would have the desired activity, amended and new claims 28 to 32, and 34 to 50 recite binding of the blood or blood fractions expressing TNFR to a surface or particle coupled to a polypeptide wherein the polypeptide comprises at least three components A and at least two components B, wherein each component A is a TNF monomer or a functional fragment or a functional variant thereof, and each component B is a peptide linker, under conditions allowing binding of TNFR in blood or blood fractions to the surface or particle; and separating the bound TNFR from the blood or blood fractions. Thus, because the amended and new claims no longer recite the TNF ligand family, and instead define component A as a TNF monomer, the claims are adequately enabled in view of the corroborating data submitted herewith and the guidance in the specification discussed in detail above.

Regarding the ground for rejection on page 13, namely, that the specification does not enable all possible TNF ligand family monomer fragments and variants with a biological activity (as component A) other than the wild-type (non-mutated) extracellular domains of TNF ligand family members and does not teach any functional or structural characteristic of the monomer variants, fragments and derivatives in the claims, again the amended and new claims recite that the polypeptide is a TNF monomer, not the TNF ligand family. As discussed above, Exhibit A shows data indicating the removal/depletion of TNFR from PBS and bovine serum using TNF monomers (scTNF) as recited in the claims, demonstrating that the scTNF was biologically active. Further, the specification discloses sequences of scTNF monomers (amino acids 79-181 of human TNF) in Figures 19, 20, 23 and 26 (page 49, line 17 to page 50, line 24, page 52, lines 7 to 23, and page 54, lines 6 to 23, respectively). Given the Declaration and Exhibit A and disclosure of scTNF monomers in the specification, it would not require undue experimentation to make or use the claimed invention.

In view of the foregoing, the skilled artisan could practice claims 28 to 32, and 34 to 50 without undue experimentation. As such, the claims are adequately enabled and

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

Claim Rejections under 35 U.S.C. 112, first paragraph, written description

The rejection of claims 28 to 45 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement is respectfully traversed. The grounds for rejection are set forth in the Office Action at pages 15 to 18.

The specification provides an adequate written description of the claims. Nevertheless, without acquiescing to the propriety of the rejection and solely in order to further prosecution of the application, claims 28 to 32, and 34 to 45 have been amended. Further, claim 33 has been cancelled herein without prejudice rendering the rejection moot. The rejection will therefore be addressed with respect to the amended and new claims.

Regarding the assertion at page 17 that the specification fails to disclose and there is no art-recognized correlation between the structure of the genus of functional fragments or functional variants of a monomer of a member of the TNF ligand family and function, amended and new claims 28 to 32, and 34 to 50 recite TNF monomer and not the TNF ligand family. Accordingly, the genus of TNF ligand family members is not the subject of the amended and new claims. Applicants respectfully direct the Examiner's attention to the Declaration under 37 C.F.R. §1.132 and accompanying Exhibit A, filed herewith. As stated above, the studies in Exhibit A confirm that a scTNF comprising three TNF monomers linked together by two peptide linkers and attached to microporous beads functions to remove/deplete TNFR as claimed.

Further, in terms of functional scTNF, the specification teaches, as acknowledged by the Examiner, generation of scTNF comprising three identical TNF monomers (amino acids 79-181 of human TNF) in Figures 19, 20, 23 and 26 (page 49, line 17 to page 50, line 24, page 52, lines 7 to 23, and page 54, lines 6 to 23, respectively). Further support in the specification for various species of TNF is found in the specification, for example, at page 56, line 13 to page 60, line 3 and Example 3 at page 64, line 13 to 65, line 7. With respect to TNF monomers, the specification teaches, as acknowledged by the Examiner, that the polypeptide or a fragment or variant thereof is functional within the meaning of the invention, provided it exhibits its biological activity of function (page 6, lines 20 to 23). Further, as

acknowledged by the Examiner, the specification discloses that the biological activity may be changed with respect to specificity or selectivity, but with retention of the basic biological activity (page 6, lines 23 to 26). Additionally, functional fragments and functional variants of TNF monomers would be known or ascertainable by the skilled artisan. In view of the specification, knowledge and skill in the art at the time of the invention, and functional fragments or functional variants of scTNF having the requisite activity, the claims are adequately described.

In view of the foregoing, the claims are adequately described under 35 U.S.C. §112, first paragraph. Accordingly, the rejection must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that the amended and new claims clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any issues, Applicants' representatives can be reached at (858) 509-4065. Please charge any fees associated with the submission of this paper to Deposit Account Number 33975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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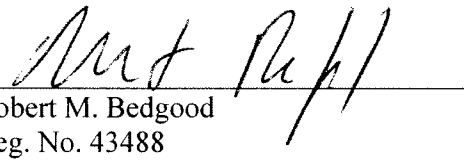
By 

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